Beyond A1C: A Practical Approach to Interpreting and Optimizing Continuous Glucose Data in Youth

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Despite significant pharmacological and technological advances in the treatment of type 1 diabetes, the majority of youth in the United States do not meet the American Diabetes Association's recommended A1C goal. Understanding and managing glycemic variability is important in children and adolescents. Because A1C provides an incomplete picture of day-to-day glycemic fluctuations, continuous glucose monitoring (CGM)-derived metrics are a promising addition to address glycemic management challenges in youth with diabetes. In this article, we discuss how to develop practical strategies to optimize the use of CGM in the pediatric population, interpret the valuable data it provides, and develop personalized and actionable treatment goals.

During childhood and adolescence, periods of rapid physical growth, neurocognitive development, sexual maturity, and the evolving dynamics in parent-child responsibilities present unique features and challenges to type 1 diabetes care in youth. Recent data from the T1D Exchange clinic registry indicate that only 14% of children and adolescents attained the current American Diabetes Association (ADA) A1C goal of <7% (1–3), and only 17% achieved the ADA's former A1C goal of <7.5% (2). Furthermore, mean A1C across all age-groups in the T1D Exchange registry worsened over time (from 2010–2012 to 2016–2018), with the highest increase in mean A1C noted in adolescents and young adults. Toddlers and young children comprise another high-risk age-group, and blinded continuous glucose monitoring (CGM) data indicate that they spend more than half of each day in a hyperglycemic range (55% of time >180 mg/dL and 30% of time >250 mg/dL), with substantial glycemic variability (4).

Current State of CGM Use in Youth

Real-time CGM (rtCGM) and intermittently scanned CGM (isCGM) systems have emerged as tools that provide extensive data on an individual's glycemic profile and the possible factors influencing it. CGM systems are minimally invasive devices with subcutaneous sensors that measure interstitial fluid glucose values approximately every 5 minutes, send personalized alerts, and provide information on the rate of change of glucose values, indicated by trend arrows. At the time of this writing, the three systems most recently approved by the U.S. Food and Drug Administration for use in youth are the Dexcom G6, Medtronic Guardian 3, and Abbott Freestyle Libre 2 (Table 1).

The prevalence of CGM use has increased across all ages in recent years, with the most significant uptake (greater than 10-fold increase) in young children (2). Advances in CGM technology, including higher sensor accuracy rates, enhanced wearability, decreased requirements for calibration, and options for data-sharing, have led to better user experiences. Improved patient-reported outcomes in technology satisfaction and burden of use have been noted when comparing recent data from the CITY (CGM Intervention in Teens and Young Adults with Type 1 Diabetes) study group (3) with previous data from the JDRF CGM study group from >10 years ago (5).

Given the increased utilization of CGM in recent years and the limitations of A1C in detecting glycemic patterns, there has been a push toward adopting newer CGM-derived glucose metrics to evaluate glycemic control. These metrics include time in range (TIR), time below range (TBR), time above range (TAR), and coefficient of variation (%CV) (Figure 1). This effort has assumed greater importance in this era of the COVID-19 pandemic, when patients are increasingly being seen via telehealth and may not have their A1C checked regularly.

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Time in Range: Why Look Beyond A1C in Pediatrics?

Age-Specific Diabetes Management Challenges

Diabetes management can be quite challenging across the pediatric age spectrum for various reasons.

Toddlers and young children are almost entirely dependent on caregivers for their diabetes management and have many unique challenges that predispose them to wide glycemic variability and potential variations in daytime-to-nighttime TIR (with lower daytime TIR) (4,6,7). Young children with type 1 diabetes tend to be picky eaters and often have unpredictable appetites, with frequent snacking or "grazing" behaviors, which makes the timing of insulin delivery and assessment of preprandial glucose levels difficult (8,9). They have random physical activity patterns and are susceptible to frequent intercurrent illnesses (6). Young children have variable insulin sensitivity resulting in unpredictable long-acting basal insulin action and require unique considerations and attention to their basal-bolus regimen (6,10,11). Moreover, behavioral attributes such as inability to articulate hypoglycemia symptoms (12,13) and parental fear of hypoglycemia, a commonly reported concern in this age-group particularly at night (14), could lead to overcompensation with hypoglycemia avoidance behaviors (15).

On the other hand, adolescents and young adults go through a challenging developmental stage that may explain their tendency to have the highest mean A1C and highest diabetic ketoacidosis rates among all age-groups (2). This stage is a time of turbulent change, with increasing autonomy, academic expectations, and shifting responsibilities of diabetes management. In particular, adolescents

TABLE 1 Comparison of Available CGM Devices Approved for Use in Youth

	Dexcom G6 (Dexcom)	Guardian 3 (Medtronic)	FreeStyle Libre 2 (Abbott)
System type (rtCGM or isCGM)	rtCGM	rtCGM	isCGM
Minimum age for approved use in children, years	2	2*	4
Need for sensor replacement	Every 10 days	Every 7 days	Every 14 days
Need for transmitter replacement	Every 3 months	Yearly, rechargeable	Every 14 days†
Transmitter and sensor size	1.68 × 0.86 × 0.33 inches	1.41 × 1.13 × 0.38 inches	1.38 inches diameter × 0.2 inches height
Need for calibration	No	Yes (twice daily)	No
Approval for nonadjunctive dosing	Yes	No	Yes
Warm-up time, hours	2	2	1
MARD, %‡	9.0	8.7–10.6§	9.3
Alert capability	Yes	Yes	Yes‖
Integration with insulin pump	Yes (Tandem t:slim ×2)	Yes (Medtronic MiniMed 670G and 630G)	No
Data-receiving app	Dexcom G6 Mobile App	Guardian Connect	Not available¶
Data-sharing/remote-monitoring app	Dexcom Follow (up to 10 people)	CareLink Connect (up to 4 people)#	Not available
Health care provider portal	Dexcom Clarity	CareLink	Not available
Interfering medications	Hydroxyurea, acetaminophen if above maximum adult dose	Acetaminophen, vitamin C injection	High-dose vitamin C, aspirin
Water resistance	8 feet for up to 24 hours	12 feet for up to 24 hours	3 feet for up to 30 minutes

Data correct as of 30 November 2020. *Approved for ages ≥2 years when used with the MiniMed 770G system, ≥7 years of age when used with the MiniMed 670G system, and ≥14 years of age when used with the MiniMed 630G. †Sensor and transmitter are integrated as one unit. ‡MARD (mean absolute relative difference) is the average of the absolute differences between reference blood glucose measurements and glucose measurements obtained by CGM. The lower the MARD, the more accurate the system. §Varies based on age, sensor location, and number of calibrations. ‖Necessary to scan to see actual glucose value and trend. ¶FreeStyle Libre 2 app is currently under regulatory review per manufacturer website. #Cannot remotely monitor if integrated with pump.

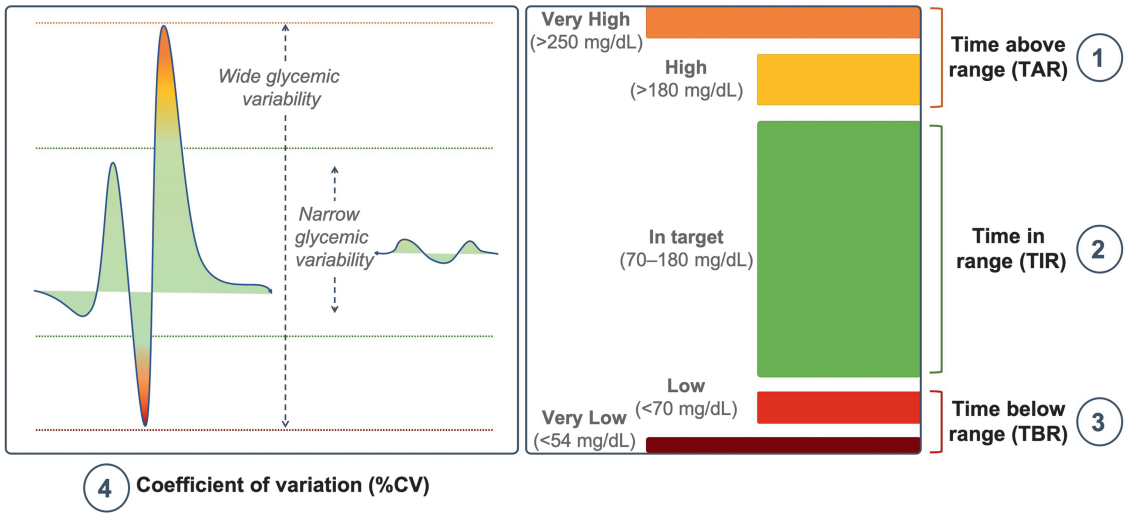

FIGURE 1 Useful CGM-derived glucose metrics in youth with type 1 diabetes.

are susceptible to a puberty-associated increase in insulin resistance (16), large appetites, poor food choices, and psychosocial factors such as diabetes burnout, family conflict, peer interactions, and body image issues that can have significant implications on glycemic control.

Limitations of A1C: How Can TIR Help Address the Gap?

Despite only being a surrogate marker of average blood glucose over the preceding 3 months, A1C continues to be the most widely used indicator of glycemic management and predictor of long-term microvascular complications (17–19). However, there is accumulating evidence that brings to light several limitations of using A1C as an isolated measure of glycemia, including nonglycemic factors that influence glycosylation of hemoglobin such as race or ethnicity (20), hemoglobinopathies (21), blood transfusions (22), and conditions that affect the red blood cell life span or turnover (e.g., anemia, lead poisoning, and asplenia/splenomegaly) (23). Significant hyperglycemia, hypoglycemia, and glycemic variability can occur even when A1C is within the target range (24).

Self-monitoring of blood glucose via fingerstick checks of capillary blood provides a snapshot of a child's glycemic status but does not offer comprehensive insight into time spent in the different glucose ranges or the magnitude of glucose variability (25). CGM-derived glucose metrics provide a more complete profile of glycemic patterns, including the frequency, duration, timing, and severity of episodes of hypoglycemia and hyperglycemia. This information can help patients, families, and the health care team identify individual factors such as variations in diet, exercise, stress, and the timing of insulin administration that may influence glycemic excursions. This ability is of particular relevance in growing children, given the potential adverse effects of recurrent and severe hypoglycemia (26,27), chronic hyperglycemia, and glucose variability (26,27) on the developing brain. Thus, to optimize neurocognitive development, it is imperative to maximize TIR in growing children and limit exposure to hypoglycemia and hyperglycemia while minimizing glucose variability.

Potential Barriers to Using CGM and TIR in Children

Regular and consistent CGM use is a prerequisite to accurately interpret glucose metrics derived from CGM data, particularly in children and adolescents, who are prone to wide glucose fluctuations (28,29). Additionally, consistent sensor usage correlates with greater improvements in A1C (5). Thus, it is essential to identify barriers to regular CGM use and design measures to address them.

We detailed potential barriers to using CGM in Figure 2. Physical barriers such as poor adhesion and skin irritation are common (30,31). Wearability issues may be particularly concerning in young children, who have limited skin space for device insertion and may not notice if the device detaches. Some patients may prefer not to have a device attached to them (32); this is a common issue in teens and young adults who have body image concerns or do not want their peers to know they have diabetes. Moreover, some patients may be fearful of CGM alerts interrupting school, extracurricular activities, and social gatherings. Remote monitoring of CGM data, despite providing an extra layer of safety, may lead to constant parental tracking and intervention and increase the likelihood of diabetes-related conflict. Baseline psychological factors such as depressive

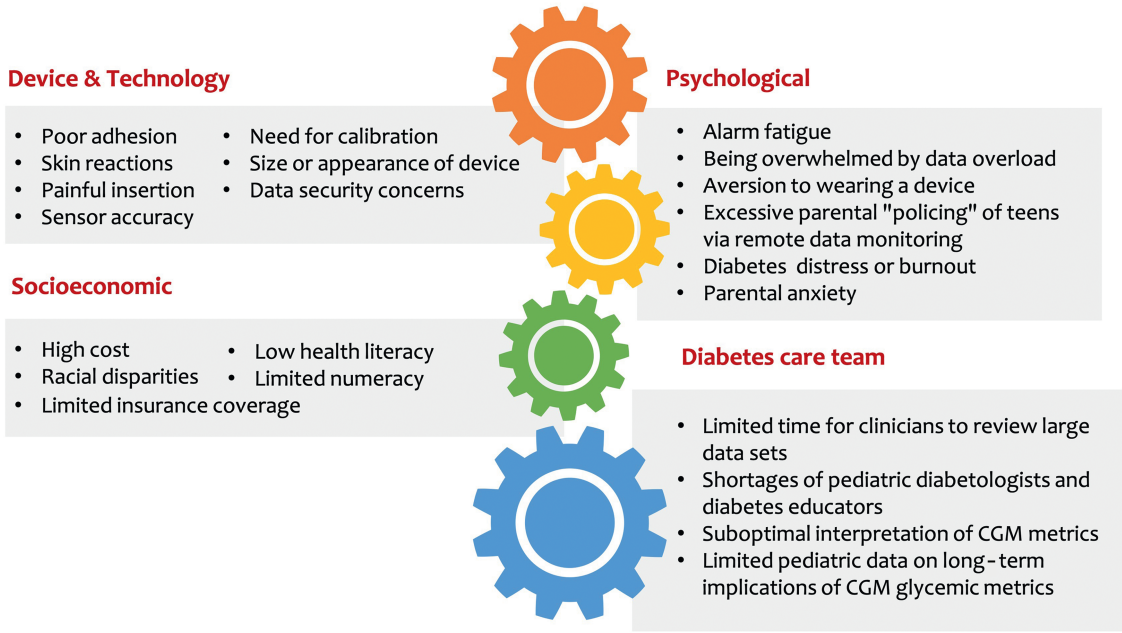

FIGURE 2 Potential barriers to optimal CGM utilization in youth.

symptoms and higher diabetes burden may predict less frequent CGM use in youth (33). Also, the constant stream of data and frequent alarms may become overwhelming for some patients and their families, contributing to anxiety, sleep disruption, and diabetes distress. Diabetes-related psychosocial stressors are already high in parents of young children with type 1 diabetes (34,35), and they may need additional resources and training.

Interpretation of TIR in Children

To optimize diabetes treatment regimens and clinical outcomes for youth with diabetes, health care providers (HCPs) need to be skilled at interpreting CGM data. In this section, we provide a practical clinical approach to analyzing CGM data (Figure 3).

1. Confirm the duration of active CGM use. Do the data provide the full picture?

Accurate assessment of CGM data requires a minimum of 2 weeks, but ideally 4 weeks, with the CGM sensor being worn for >70% of the time (29,36). Studies show that CGM use >70% of the time over the most recent 14 days strongly correlates with 3 months of mean glucose, TIR, and hyperglycemia metrics but has a weaker correlation with glycemic variability and hypoglycemia metrics (28,29,36). Children with wide-ranging glycemic trends, frequent hypoglycemia, or inadequate glycemic control require extended CGM data periods, up to 4 weeks, for more accurate interpretation (29). This is an important consideration when reviewing the data of preschool-age children, who are prone to wide glycemic variability, or adolescents, who are prone to poor glycemic control (7,29).

With isCGM devices, a full 24-hour data profile is captured only if the sensor is scanned at least every 8 hours (37). Evidence on the accuracy of isCGM data compared with rtCGM is subject to variable confounders that make reliable clinical comparisons challenging (37). Recent evidence in the pediatric population suggests better accuracy of 2 weeks of data using rtCGM and recommended the use of 4 weeks of data when interpreting isCGM data (29).

2. Review informative and actionable CGM-derived glucose metrics

Metrics Based on Time Spent in Various Glucose Ranges

The most recent international consensus on TIR recommends using times in which glucose values are within particular ranges as a metric of glycemic control (28). As described above, the three key metrics in clinical practice are TIR, TBR, and TAR. Each metric can be expressed as a percentage of CGM readings or as an average number of hours and minutes spent in each range per day. These metrics are appropriate and useful to inform and guide diabetes treatment decisions, as discussed below (28).

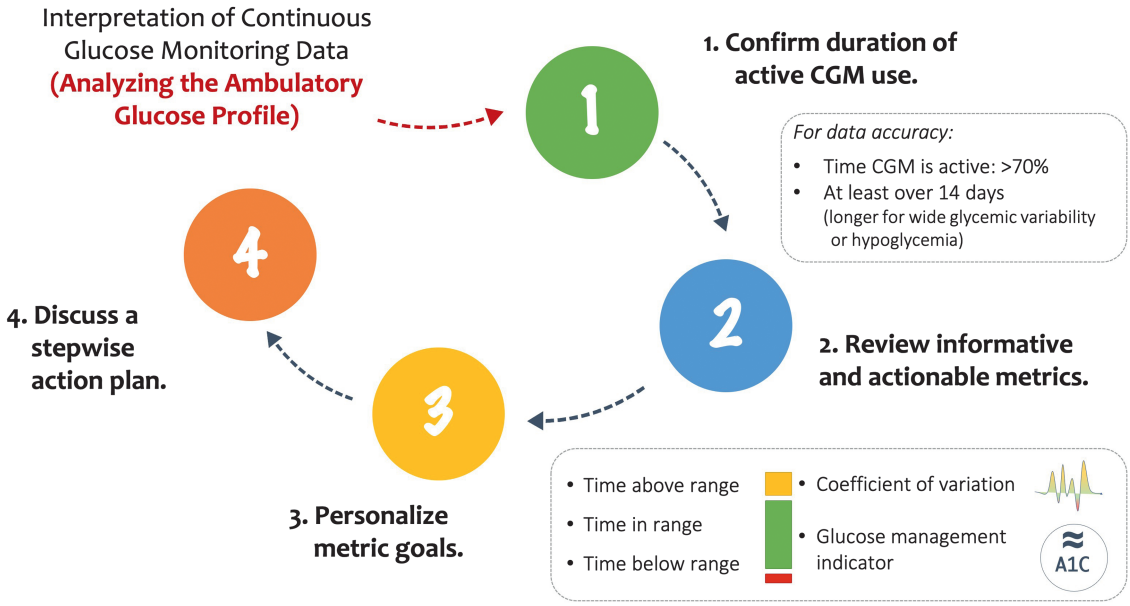

FIGURE 3 Practical approach to interpreting TIR metrics in youth with type 1 diabetes.

Metrics of Glycemic Variability

The preferred metric for assessing glycemic variability is %CV, with a therapeutic goal of ≤36 and >36% considered suboptimal (28). The %CV metric may be useful in predicting hypoglycemia risk, as a higher %CV is strongly associated with more time in the hypoglycemia range in children (7), whereas a %CV <25% poses an extremely low risk of severe hypoglycemia (38).

Glucose Management Indicator

The glucose management indicator (GMI) is calculated from average CGM-derived glucose values and provides an estimate of A1C (17,28). However, it is important to understand the potential discordance between GMI and laboratory-derived A1C levels caused by the effect of variability in the life span of red blood cells and other factors. An individual's GMI can either overestimate, underestimate, or match A1C. This difference between GMI and A1C for an individual is relatively stable over time, allowing personalized interpretation of GMI. For example, if a child has a higher GMI than A1C, then GMI will usually continue to be higher than A1C on repeated comparisons over time, and vice versa (17). Table 2 provides estimate correlations of A1C with TIR (28,39,40). Laboratory-derived A1C (using an NGSP-certified method that is standardized to the Diabetes Control and Complications Trial assay) remains the primary measure guiding the risk of developing long-term diabetes micro- and macrovascular complications until more robust evidence becomes available connecting GMI and other CGM-derived glucose metrics to risks of diabetes complications (17–19).

3. Personalize CGM-derived glucose metric goals

It is necessary to individualize goals to facilitate both effective and safe glucose control. The overall goal in clinical practice is to increase TIR and reduce TBR while minimizing glycemic variability (28,41). A general approach is to prioritize hypoglycemia metrics first to reduce severe hypoglycemia risk, then address hyperglycemic metrics to improve TIR, and finally minimize glycemic variability (41). Metric goals in the pediatric population are extrapolated from the adult literature (28), as shown in Figure 4.

Targets for CGM-Derived Glucose Metrics in Youth

The International Consensus Report for TIR recommends ideal targets for times in the various glycemic ranges based on correlations with an A1C goal ≤7% in adults (28). In children, adult targets can be used as a guide as long as they align with the ADA recommendation to aim for the lowest achievable A1C (<7 or <6.5%) without exposure to significant hypoglycemia or negative impact on well-being or burden of care (Figure 4). These targets should be individualized for each patient and reassessed over time to optimize effectiveness while reducing risks (1,28).

Considerations for High-Risk Populations

Children with hypoglycemia unawareness and those who have a history of severe hypoglycemia are vulnerable to elevated risks of hypoglycemia (1,6). For these children, the

TABLE 2 Estimated Relationship Between A1C and TIR Based on Adult Studies

TIR (70–180 mg/dL)			
Percentage of CGM Readings	Time per Day	A1C, % (39)	A1C, % (40)
20	4 hours, 48 minutes	9.4	10.6
30	7 hours, 12 minutes	8.9	9.8
40	9 hours, 36 minutes	8.4	9.0
50	12 hours	7.9	8.3
60	14 hours, 24 minutes	7.4	7.5
70	16 hours, 48 minutes	7.0	6.7
80	19 hours, 12 minutes	6.5	5.9
90	21 hours, 36 minutes	6.0	5.1

Adapted from ref. 28.

ADA suggests considering a higher A1C goal (7.5–8%), which equates to TIR of 50–60% (1,28). We extrapolated this target TIR based on the consensus report for the elderly and high-risk population (28), emphasizing reducing hypoglycemia before optimizing TIR.

Targets for Glycemic Variability

Limited evidence in pediatrics suggests that using a more stringent glycemic variability target than the adult target of <36%CV could decrease hypoglycemic risk in children (7). Therefore, diabetes management strategies to lower %CV may also reduce the risk of hypoglycemia in children.

4. Discuss an achievable, stepwise action plan with personalized shared decisions

For a more prominent clinical impact in interpreting CGM data, we recommend focusing on small, achievable steps that are personalized to meet each patient's or family's needs and capabilities.

Importance of Setting Realistic, Achievable Goals

Setting small, achievable goals can enhance coping with diabetes and motivate successful changes in diabetes care behaviors (28,42,43). A shared decision-making approach in setting realistic goals with the patient and family can empower them to make continuous changes in daily life and maximize CGM benefits (43). Moreover, it is useful to communicate goals with families by using practical and meaningful CGM metrics (28). For example, discussing strategies to reduce hypoglycemia at night may be more meaningful to families than setting a goal of <1% TBR.

Stepwise, Individualized Approach

Providers can encourage families to take incremental steps and emphasize that even small changes can yield clinically significant glycemic benefits. For example, a 5% increase in TIR equates to an additional 1 hour, 12 minutes of glucose being within target each day. Studies show that an improvement in TIR of 10% could reduce A1C by 0.5–0.8% (28,39,40).

Optimization of TIR in Children

The following sections discuss factors that can facilitate or hinder optimal glycemic control in an ambulatory clinical setting. HCPs may consider these factors when individualizing care for their pediatric patients and counseling families.

Facilitators for Achieving Optimal Glycemic Targets

Use of Insulin Pump With CGM

Recent advanced technologies such as sensor-augmented pump (SAP) therapy or hybrid closed-loop (HCL) insulin delivery systems may facilitate improvement in TIR. A recent large study compared TIR in children using SAP therapy with rtCGM to those treated with multiple daily insulin injections with rtCGM in the real world and noted a higher TIR in the SAP group (61 vs. 56%) (44). It also highlighted an association of rtCGM with better glycemic metrics than isCGM regardless of insulin delivery method, including higher TIR, lower TBR, and reduced %CV (44). Randomized controlled trials in children suggest that HCL systems have superiority in achieving better TIR (45–47), up to 67 ± 10% compared with 51 ± 13% with SAP therapy (45).

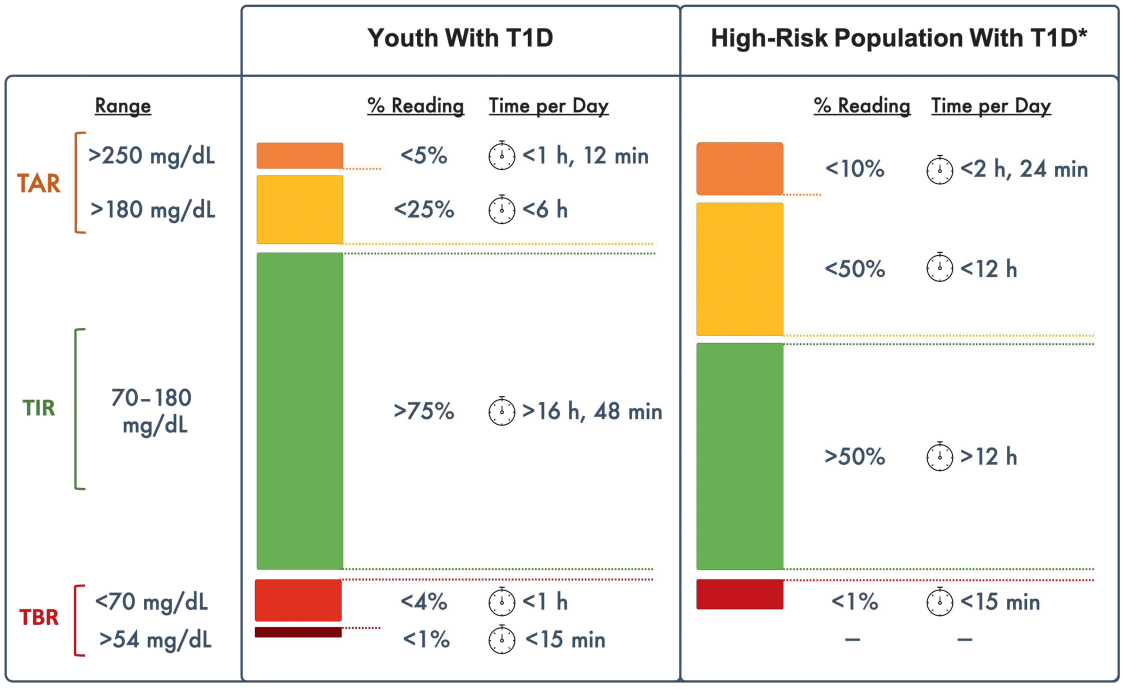

FIGURE 4 Targets of CGM-derived glucose metrics in youth with type 1 diabetes. *Children with hypoglycemia unawareness and history or severe hypoglycemia. h, hour(s); min, minutes; T1D, type 1 diabetes.

Interacting With CGM Data to Enable Real-Time Management Decisions

It is essential to empower families to adopt a dynamic approach to diabetes, through which they are encouraged and counseled about making real-time decisions based on CGM data. HCPs can inform families about the benefits of interacting with CGM data to take a proactive role in improving glycemic control. Dynamic diabetes management necessitates awareness of all of the variables affecting glucose trends and incorporating CGM trend arrows to make informed decisions. Figure 5 enumerates practical tips to guide families in dynamic CGM utilization (42,48,49). Based on rates of glucose change on Dexcom sensors, the 30–60–90 Rule allows users to incorporate glucose trend arrows (rising or falling) in anticipation of the predicted change in glucose 30 minutes in the future. Users can add 30, 60, or 90 mg/dL to the current glucose value for a diagonal arrow up, single arrow up, or double arrow up, respectively, or subtract 30, 60, or 90 mg/dL from the current glucose value for a diagonal arrow down, a single arrow down, or a double arrow down, respectively. For example, if the sensor glucose is 250 mg/dL with a single arrow up, the patient would use 310 mg/dL when calculating the correction insulin dose; by contrast, if the sensor glucose is 250 mg/dL with a single arrow down, the patient would use 190 mg/dL when calculating the correction dose.

Language Matters

The language used by HCPs can be a powerful tool to motivate patients and foster positive patient-provider relationships. Language should focus on strength, respect, and imparting hope. HCPs need to embrace a personalized approach and be mindful of conveying empathy and understanding in their communication of CGM data and glycemic targets (43,50).

Barriers to Achieving Optimal Glycemic Targets

Alerts/Alarm Fatigue

CGM systems can alert patients and families to actual or impending hypoglycemia, hyperglycemia, or rapidly changing trends. Although this feature helps make real-time decisions to improve glycemic control, it may become a psychosocial burden (31,51). In our clinical practice, we encourage families to input individualized alert settings such that the system provides actionable alarms that are continuously revisited and adjusted in consideration of the patient's glycemic control, age, and hypoglycemia awareness and the impact of alerts and alarms on daily life. Families are encouraged to set realistic alerts to avoid alarm fatigue, a common factor in CGM discontinuation (31,52).

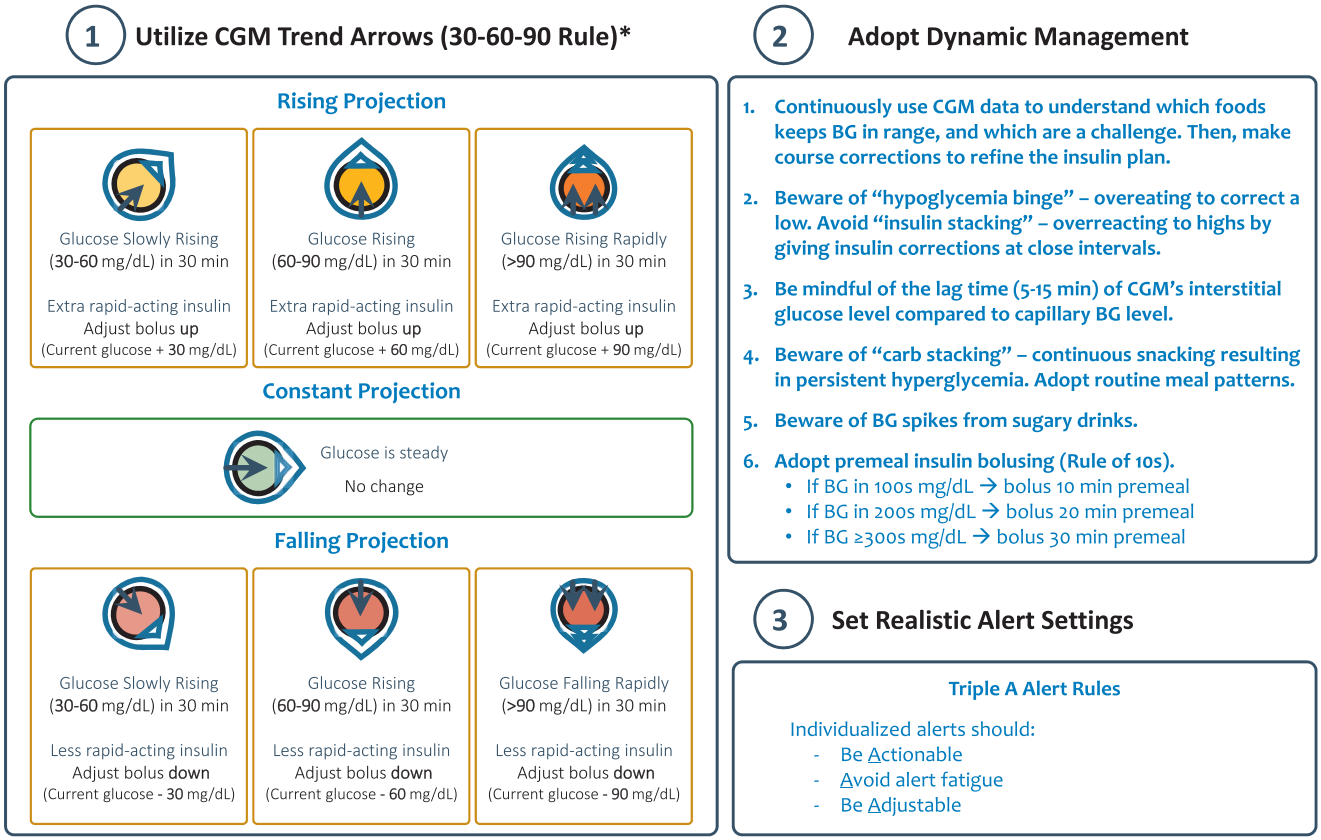

FIGURE 5 Practical tips to guide families in CGM use. *To determine the rapid-acting insulin dose, adjust the current glucose level by adding or subtracting 30, 60, or 90 mg/dL depending on glucose arrow tends. BG, blood glucose; carb, carbohydrate; min, minutes.

Unrealistic Expectations

HCPs are encouraged to discuss expectations of CGM use with their patient families. Although CGM has many psychological benefits in improving quality of life and decreasing fear of hypoglycemia, some families may become overwhelmed by the abundance of glucose data and feel stress about real-time glycemic excursions. HCPs need to be attentive to families' problem-solving abilities, anxiety levels, and comfort with technology to enable a positive CGM experience (31,51). In the SENCE (Strategies to Enhance New CGM Use in Early Childhood) study, family-based interventions addressing potential behavioral barriers to CGM use in young children and teaching parents skills to navigate these challenges improved the consistency of CGM use, psychological outcomes, and technology satisfaction (53).

Inequitable Access to Technologies

Despite the increase in the use of diabetes technologies among youth with type 1 diabetes, data from national and international diabetes registries raise concerns about inequities in device uptake based on socioeconomic status and race/ethnicity. Youth with type 1 diabetes from lower–socioeconomic status households may be at a systematic disadvantage, hindering their adoption of diabetes technologies and potentially widening existing disparities in diabetes outcomes (54). We may expect CGM usage rates to increase in coming years with continued advancements in device design and accuracy; potentially expanding insurance coverage, including public insurance; and improving patient and HCP experiences with enhanced ease of Cloud-based data uploading platforms and integration of CGM with insulin delivery devices.

Conclusion

CGM and the comprehensive glucose metrics it provides have emerged as tools that can help better understand glucose patterns and develop personalized, specific goals for youth living with diabetes. However, affordability and access to technologies continue to be significant limiting factors. Decreasing the cost of devices, expanding insurance coverage, and addressing health care disparities is

crucial for widening CGM uptake. Current evidence on optimal targets for CGM-derived glucose metrics and their impact on long-term complications and patient-reported outcomes in the pediatric population are promising but limited. Further research in this area and the inclusion of TIR and other CGM-derived metrics as outcome measures in clinical trials are essential to bridge the knowledge gap.

DUALITY OF INTEREST

D.J.D. is an independent consultant for Dexcom and Insulet and receives research supplies from both companies. No other potential conflicts of interest relevant to this article were reported.

AUTHOR CONTRIBUTIONS

I.A.-G. and S.M. wrote the first draft of the manuscript. S.K.L. and D.J.D. contributed to the discussion and reviewed and edited the manuscript. D.J.D. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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